Jan please

116997

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: S. Kumar Examiner # : 69594 Date: 3/16/04
Art Unit: 1631 Phone Number 30 571 272 0640 Serial Number: 10/058,192
Mail Box and Bldg/Room Location: REM 5D61 5C18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MG

****

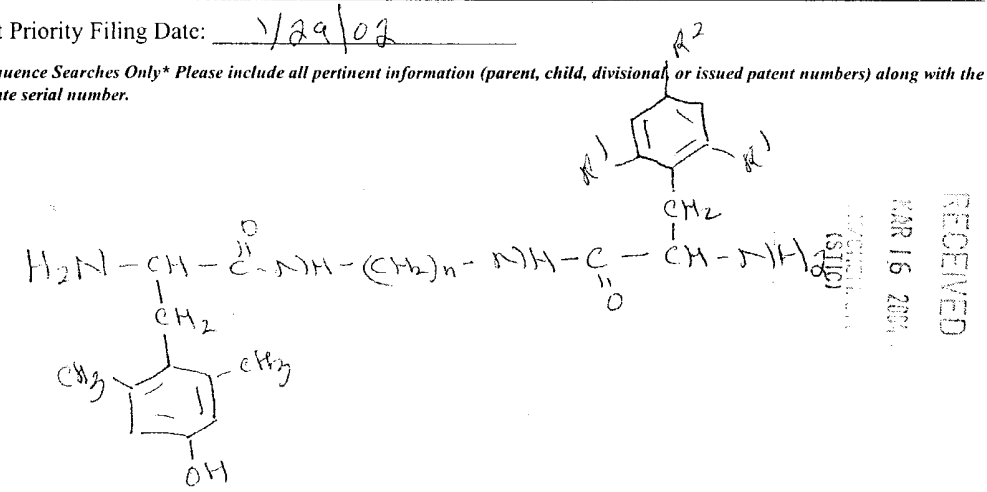
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Opioid derivatives

Inventors (please provide full names): Yoshio Okada et al

Earliest Priority Filing Date: 1/29/02

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**



R^1 is H, CH_3
R^2 is H, OH
n is 1 to 8 provided that R^1 is H when R^2 is H

****

STAFF USE ONLY

Searcher: _____
Searcher Phone #: 22504
Searcher Location: _____
Date Searcher Picked Up: 3/16
Date Completed: 3/16
Searcher Prep & Review Time: _____
Clerical Prep Time: 10
Online Time: + 20

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) ✓
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

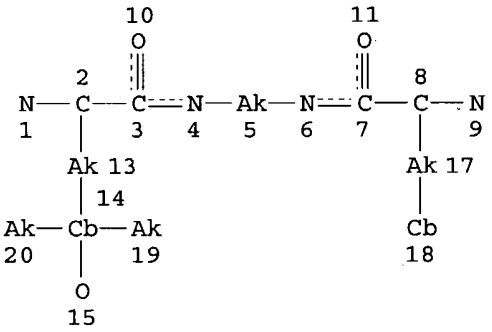
STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 116997

TO: Shailendra Kumar **Location: 5d61 / 5c18** **Tuesday, March 16, 2004** **Art Unit: 1621** **Phone: 272-0640** **Serial Number: 10 / 058192**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

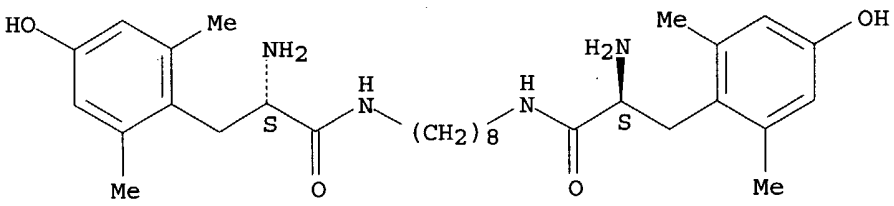
Search Notes

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 16:06:40 ON 16 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   15 MAR 2004  HIGHEST RN 663595-21-9
DICTIONARY FILE UPDATES:  15 MAR 2004  HIGHEST RN 663595-21-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l25
L3                STR
```




```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  18

STEREO ATTRIBUTES: NONE
L21               SCR 1569
L24            18 SEA FILE=REGISTRY SSS FUL L3 AND L21
L25            16 SEA FILE=REGISTRY ABB=ON  PLU=ON  L24 NOT (156892-58-9 OR
                  156893-23-1)


=> d his

     (FILE 'HOME' ENTERED AT 15:50:27 ON 16 MAR 2004)
                  SET COST OFF

     FILE 'REGISTRY' ENTERED AT 15:50:38 ON 16 MAR 2004
L1                STR
L2              0 S L1
```

```
L3              STR L1
L4            0 S L3
L5              STR L1
L6            0 S L5 CSS
L7              STR L5
L8            0 S L7
L9              STR L7
L10             STR L9
L11           0 S L10 CSS
L12             SCR 2127 OR 2043
L13           0 S L10 NOT L12 CSS SAM
L14             STR L10
L15           0 S L14 CSS
L16           0 S L14 NOT L12 CSS SAM
L17             SCR 2039 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 OR 2052 OR 205
L18           0 S L14 NOT L17 CSS SAM
L19             STR L14
L20           0 S L19 CSS SAM
L21             SCR 1569
L22           0 S L3 AND L21 CSS SAM
L23           0 S L3 AND L21 SAM
L24          18 S L3 AND L21 FUL
                SAV L24 KUMAR058/A
L25          16 S L24 NOT (156892-58-9 OR 156893-23-1)
L26           2 S L24 NOT L25

     FILE 'HCAOLD' ENTERED AT 16:05:19 ON 16 MAR 2004
L27           0 S L25
L28           0 S L26

     FILE 'HCAPLUS' ENTERED AT 16:05:22 ON 16 MAR 2004
L29           4 S L25
L30           1 S L26
L31           4 S L29,L30
L32           3 S L31 AND (OKADA Y? OR TSUDA Y? OR YOKOI T? OR BRYANT S? OR LAZ
L33           1 S L31 AND TEIKOKU?/PA,CS
L34           4 S L31-L33

     FILE 'USPATFULL, USPAT2' ENTERED AT 16:06:24 ON 16 MAR 2004
L35           3 S L25 OR L26

     FILE 'REGISTRY' ENTERED AT 16:06:40 ON 16 MAR 2004

=> d ide can tot l25

L25  ANSWER 1 OF 16  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   649757-31-3  REGISTRY
CN   Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-
     dimethyl-, dihydrochloride, (αS,α'S)- (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C30 H46 N4 O4 . 2 Cl H
SR   CA
LC   STN Files:   CA, CAPLUS
CRN  (573703-41-0)

Absolute stereochemistry.
```



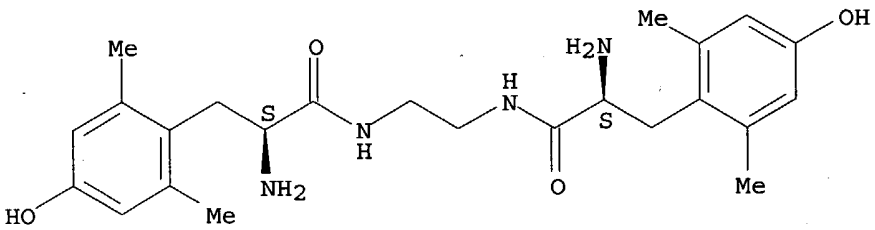
●2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

L25 ANSWER 2 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 649757-28-8 REGISTRY
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (573703-38-5)

Absolute stereochemistry.



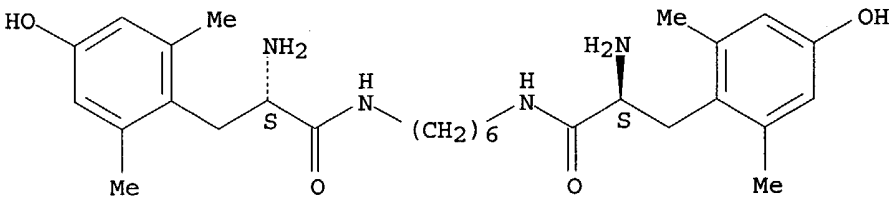
●2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

L25 ANSWER 3 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-70-9 REGISTRY
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H42 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



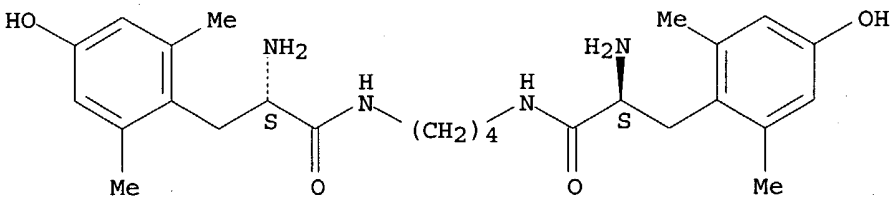
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 4 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-67-4 REGISTRY
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H38 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



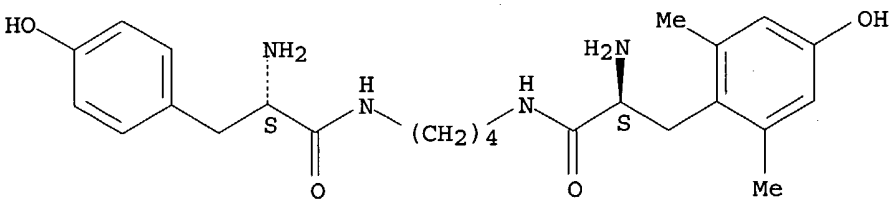
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 5 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-65-2 REGISTRY
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



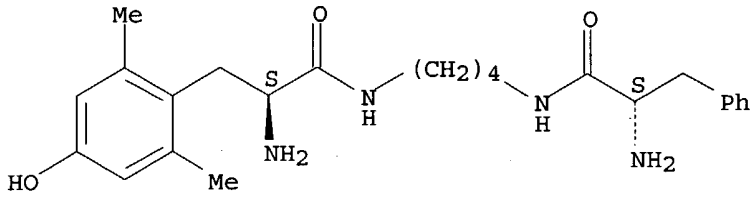
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 6 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-61-8 REGISTRY
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

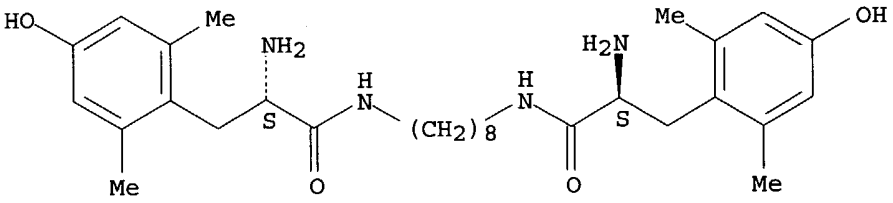
REFERENCE 1: 139:173182

L25 ANSWER 7 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-42-1 REGISTRY
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H46 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

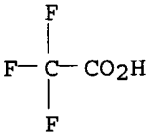
CRN 573703-41-0
CMF C30 H46 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



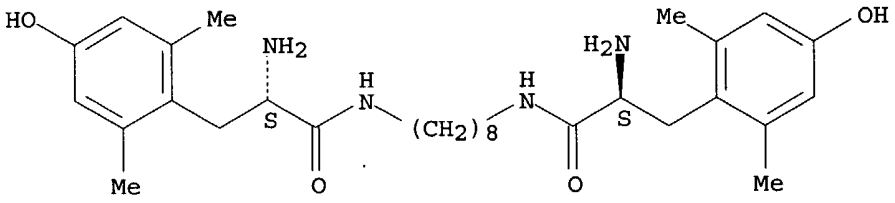
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

REFERENCE 2: 139:164977

L25 ANSWER 8 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-41-0 REGISTRY
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H46 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

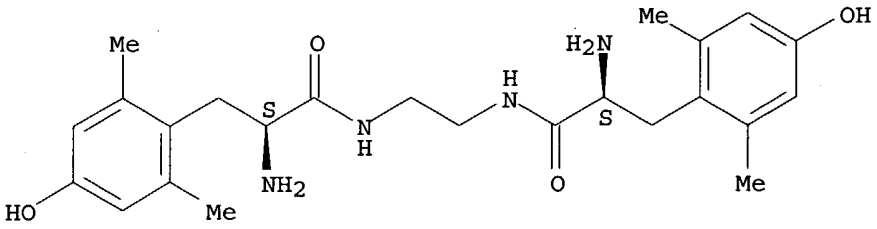
L25 ANSWER 9 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-39-6 REGISTRY

CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

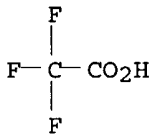
CRN 573703-38-5
CMF C24 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

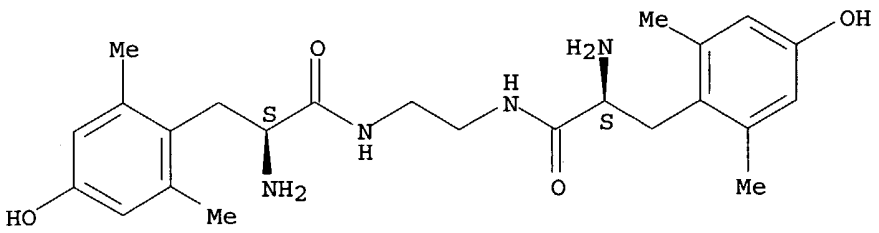


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:164977

L25 ANSWER 10 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-38-5 REGISTRY
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



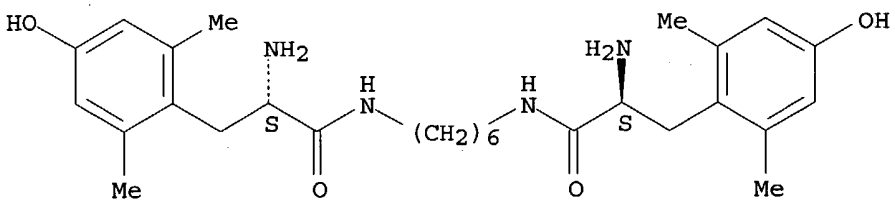
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 11 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-36-3 REGISTRY
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H42 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-70-9)

Absolute stereochemistry.



●2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

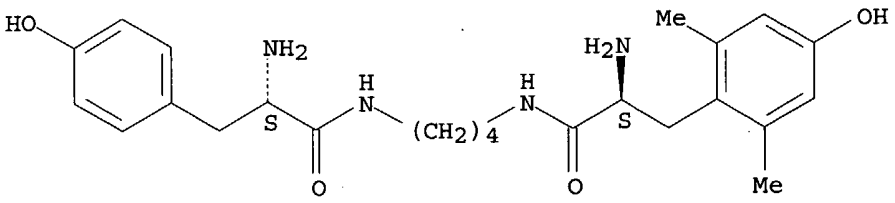
REFERENCE 1: 140:128650

REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 12 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-34-1 REGISTRY
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-65-2)

Absolute stereochemistry.



●2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

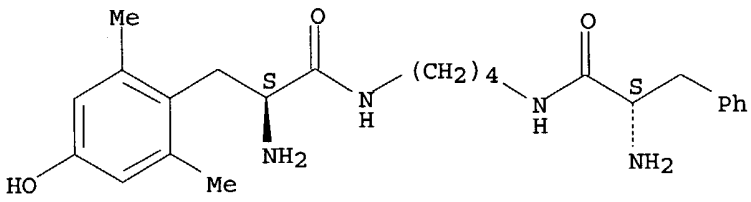
REFERENCE 1: 140:128650

REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 13 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-31-8 REGISTRY
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-61-8)

Absolute stereochemistry.



●2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

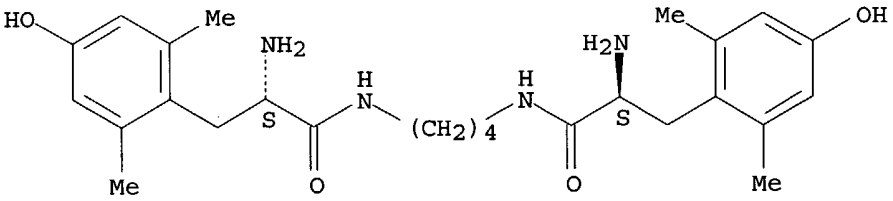
REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 14 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-27-2 REGISTRY
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-

dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H38 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-67-4)

Absolute stereochemistry.



●2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

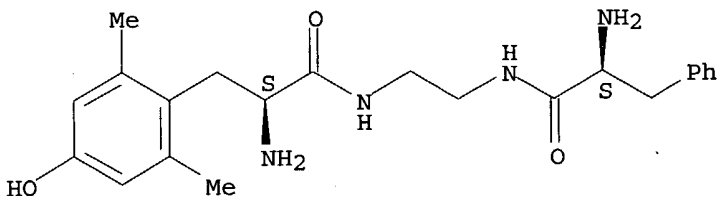
REFERENCE 1: 140:128650

REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 15 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 156893-25-3 REGISTRY
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H30 N4 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

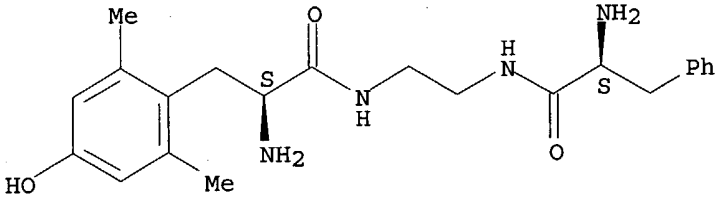
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

L25 ANSWER 16 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 156892-66-9 REGISTRY

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H30 N4 O3 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (156893-25-3)

Absolute stereochemistry.



●2 HCl

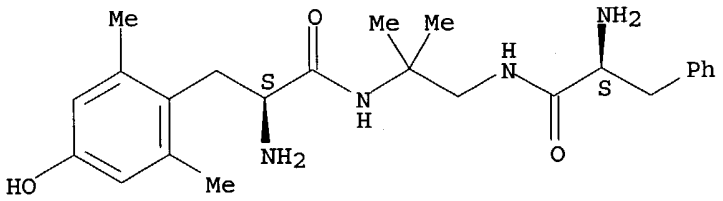
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

=> d ide can tot l26

L26 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 156893-23-1 REGISTRY
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

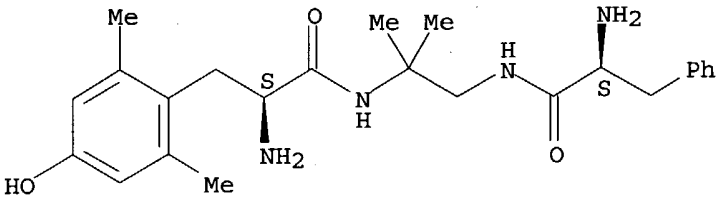
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

L26 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN

RN 156892-58-9 REGISTRY
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (156893-23-1)

Absolute stereochemistry.



●2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

=> fil uspatall
FILE 'USPATFULL' ENTERED AT 16:07:00 ON 16 MAR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 16:07:00 ON 16 MAR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l35 bib abs hitstr tot

L35 ANSWER 1 OF 3 USPATFULL on STN
AN 2003:244888 USPATFULL
TI Opioid derivative
IN Okada, Yoshio, Akashi-shi, JAPAN
Tsuda, Yuko, Akashi-shi, JAPAN
Yokoi, Toshio, Akashi-shi, JAPAN
Bryant, Sharon D., Chapel Hill, NC, UNITED STATES
Lazarus, Lawrence H., Durham, NC, UNITED STATES
PI US 2003171302 A1 20030911
AI US 2002-58192 A1 20020129 (10)
DT Utility
FS APPLICATION
LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 966
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 1. A peptide derivative represented by the following formula (1) or a salt thereof; ##STR1##

, wherein R.sup.1 is hydrogen atom or methyl group, R.sup.2 is hydrogen atom or hydroxy group and n is an integer of 1-8, provided that R.sup.1

is hydrogen atom when R.sup.2 is hydrogen atom, which has specific and high binding affinity with the μ-opioid receptor.

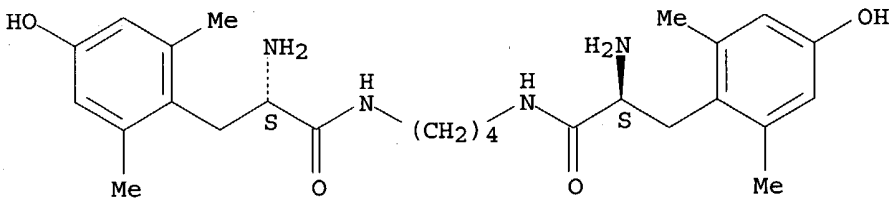
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **573703-27-2P 573703-31-8P 573703-34-1P**
573703-36-3P 573703-39-6P 573703-42-1P
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)

RN 573703-27-2 USPATFULL

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

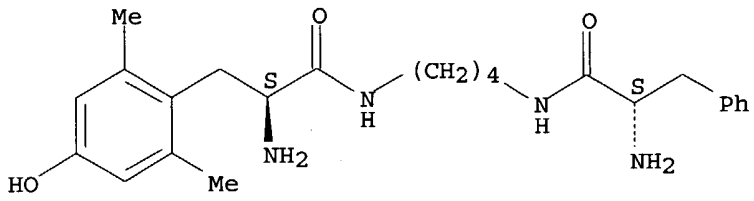


●2 HCl

RN 573703-31-8 USPATFULL

CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

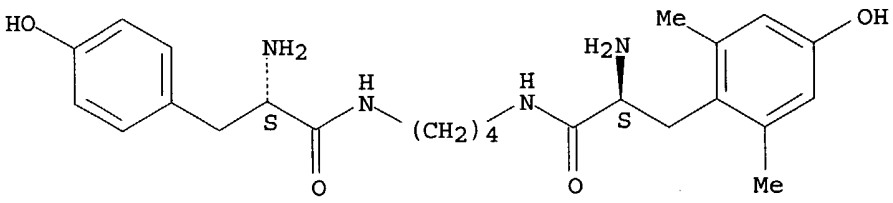


●2 HCl

RN 573703-34-1 USPATFULL

CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

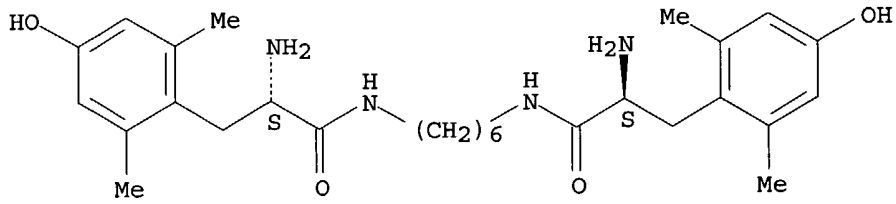
Absolute stereochemistry.



●2 HCl

RN 573703-36-3 USPATFULL
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



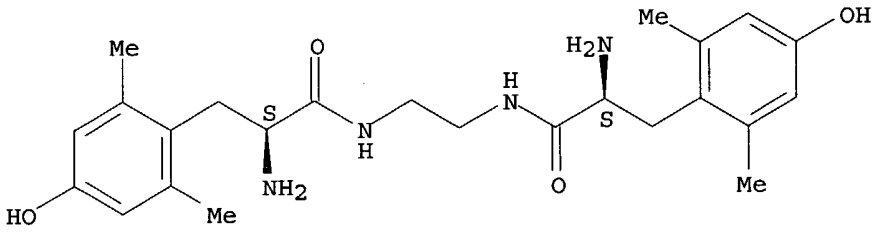
●2 HCl

RN 573703-39-6 USPATFULL
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

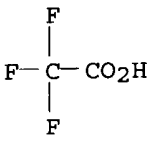
CRN 573703-38-5
CMF C24 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

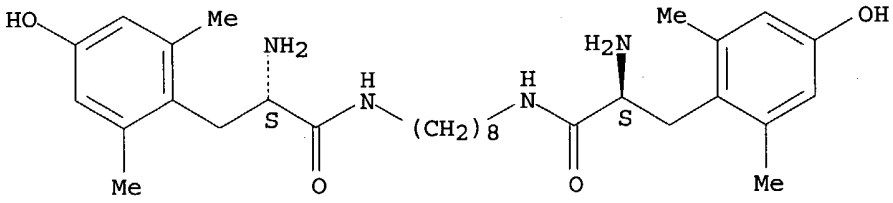


RN 573703-42-1 USPATFULL
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

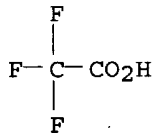
CRN 573703-41-0
CMF C30 H46 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

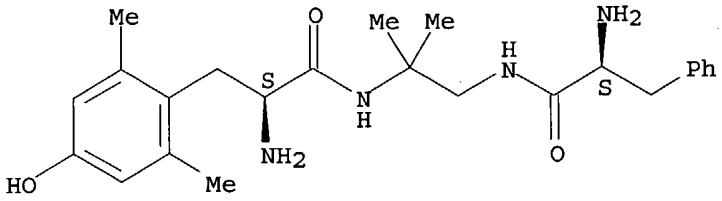


L35 ANSWER 2 OF 3 USPATFULL on STN
AN 94:99903 USPATFULL
TI Substituted tyrosyl diamide compounds
IN Hansen, Jr., Donald W., Skokie, IL, United States
Chandrakumar, Nizal S., Vernon Hills, IL, United States
Peterson, Karen B., Vernon Hills, IL, United States
Tsymbalov, Sofya, Des Plaines, IL, United States
Husa, Robert K., Gurnee, IL, United States
PA G. D. Searle & Co., Chicago, IL, United States (U.S. corporation)
PI US 5364850 19941115
AI US 1993-125897 19930924 (8)
RLI Division of Ser. No. US 1992-886276, filed on 20 May 1992, now patented, Pat. No. US 5272175
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.
LREP Hastreiter, Roberta L., Williams, Roger A.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 2287
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides substituted tyrosyl diamide compounds of general Formula I: ##STR1## and the pharmaceutically-acceptable salts thereof, which are useful for inducing analgesia in animals, pharmaceutical compositions comprising a pharmaceutically-acceptable carrier and a compound of Formula I, and a method for inducing analgesia in an animal in need thereof comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **156892-58-9P 156892-66-9P 156893-23-1P**
156893-25-3P
(preparation of, as analgesic)
RN 156892-58-9 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

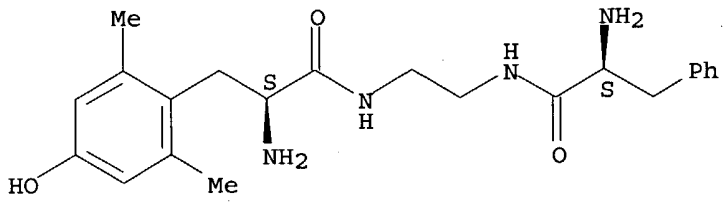
Absolute stereochemistry.



●2 HCl

RN 156892-66-9 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

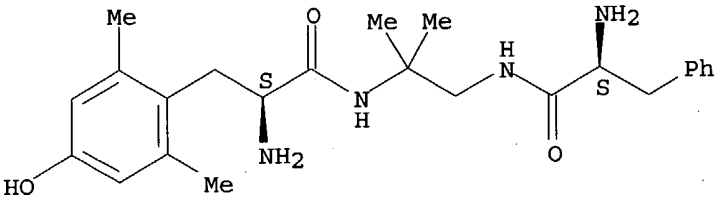
Absolute stereochemistry.



●2 HCl

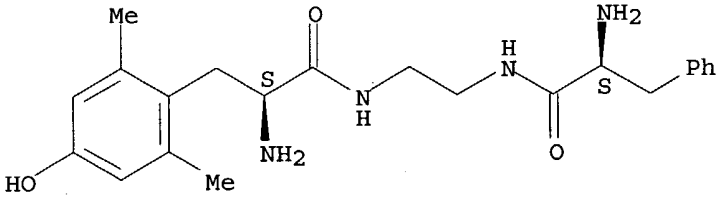
RN 156893-23-1 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156893-25-3 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

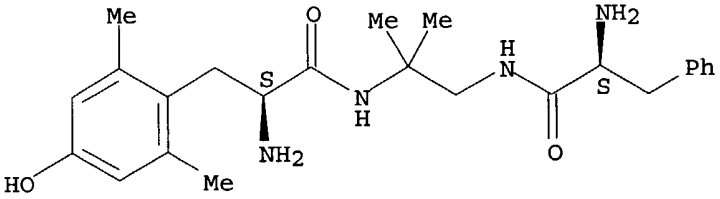
Absolute stereochemistry.



L35 ANSWER 3 OF 3 USPATFULL on STN
AN 93:107046 USPATFULL
TI Substituted tyrosyl diamide compounds
IN Hansen, Jr., Donald W., Skokie, IL, United States
Chandrakumar, Nizal S., Vernon Hills, IL, United States
Peterson, Karen B., Vernon Hills, IL, United States
Tsymbalov, Sofya, Des Plaines, IL, United States
Husa, Robert K., Vernon Hills, IL, United States
PA G. D. Searle & Co., Chicago, IL, United States (U.S. corporation)
PI US 5272175 19931221
AI US 1992-886276 19920520 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.
LREP Hastreiter, Roberta L., Williams, Roger A.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2547
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides substituted tyrosyl diamide compounds of general Formula I: ##STR1## and the pharmaceutically-acceptable salts thereof, which are useful for inducing analgesia in animals, pharmaceutical compositions comprising a pharmaceutically-acceptable carrier and a compound of Formula I, and a method for inducing analgesia in an animal in need thereof comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **156892-58-9P 156892-66-9P 156893-23-1P 156893-25-3P**
(preparation of, as analgesic)
RN 156892-58-9 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

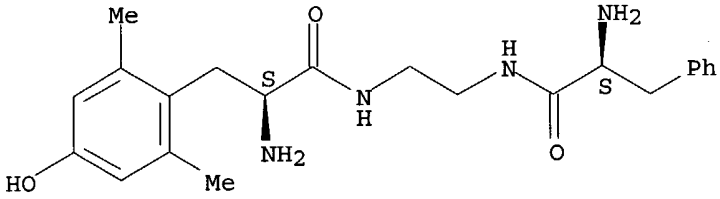
Absolute stereochemistry.



●2 HCl

RN 156892-66-9 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

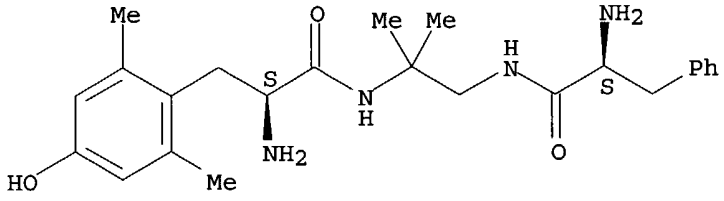
Absolute stereochemistry.



●2 HCl

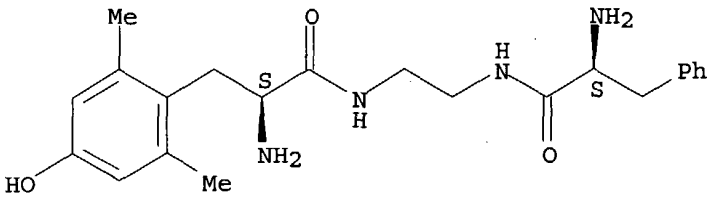
RN 156893-23-1 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156893-25-3 USPATFULL
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:07:14 ON 16 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 16 Mar 2004  VOL 140 ISS 12
FILE LAST UPDATED: 15 Mar 2004  (20040315/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d all hitstr tot l34

L34  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:610409  HCAPLUS
DN   139:164977
ED   Entered STN:  08 Aug 2003
TI   Preparation of tyrosine alkanediamide derivs. having μ-opioid binding
     affinity
IN   Okada, Yoshio; Tsuda, Yuko; Yokoi, Toshio;
     Bryant, Sharon D.; Lazarus, Lawrence H.
PA   Teikoku Seiyaku Co., Ltd., Japan
SO   PCT Int. Appl., 50 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07C237-20
     ICS  A61K031-165; A61P025-04; A61P043-00
CC   34-3 (Amino Acids, Peptides, and Proteins)
     Section cross-reference(s): 1, 2
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2003064375     A1    20030807       WO 2003-JP516    20030122
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
```

PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG

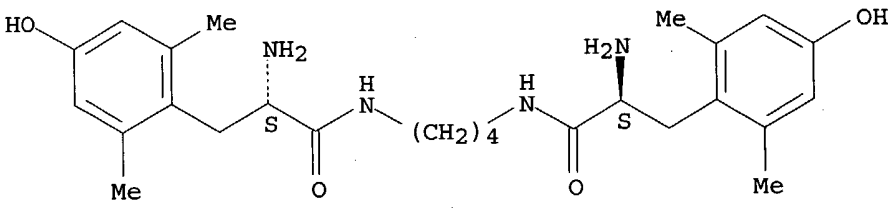
US 2003171302 A1 20030911 US 2002-58192 20020129
PRAI US 2002-58192 A 20020129
OS MARPAT 139:164977
AB Peptide derivs. 2,6,4-Me2(HO)C6H2CH2CH(NH2)CONH(CH2)nNHCOCH(NH2)CH2C6H2R12 R2-2,6,4 (R1 = H or Me; R2 = H or OH; n = 1-8, provided that R1 is H when R2 is H), having specific and high binding affinity with the μ-opioid receptor, were prepared Thus, 1,4-bis(Dmt-amino)butane.2HCl and 1,6-bis(Dmt-amino)hexane.2HCl (Dmt = 2,6-dimethyl-L-tyrosine residue) were prepared and shown to have δ- and μ-receptor affinities of 133 ± 18 nM/0.38 ± 0.02 nM and 53.4 ± 14.8 nM/0.041 ± 0.003 nM, resp., and to have analgesic activity via the μ-opioid receptor.
ST tyrosine alkanediamide prepn opioid binding analgesic
IT Analgesics
Nerve, disease
Pain
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT Opioids
Peptides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT Amino acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(μ-opioid; preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT **573703-27-2P 573703-31-8P 573703-34-1P**
573703-36-3P 573703-39-6P 573703-42-1P
573703-44-3P 573703-46-5P 573703-49-8P 573703-52-3P 574705-94-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT 107-15-3, 1 2 Diaminoethane, reactions 110-60-1, 1 4 Diaminobutane
124-09-4, 1 6 Diaminohexane, reactions 373-44-4, 1 8 Diaminooctane
3978-80-1 13734-34-4 35661-40-6 68076-36-8 126312-63-8
147688-40-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
IT 81649-48-1P 99953-00-1P 573703-26-1P 573703-28-3P 573703-30-7P
573703-32-9P 573703-33-0P 573703-35-2P 573703-37-4P 573703-40-9P
573703-43-2P 573703-45-4P 573703-47-6P 573703-50-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Fukumizu, J; 120th Annual Conference of the Pharmaceutical Society of Japan

in Gifu 2000
(2) Fukumizu, J; Nippon Yakugakkai Dai 120 Nenkai Yoshishu, Gifu 2000, P129
(3) G D Searle & Co; US 5272175 A 1993 HCAPLUS
(4) Okada, Y; Tetrahedron 1999, V55(50), P14391 HCAPLUS
(5) Teikoku Seiyaku Kabushiki Kaisha; JP 200269059 A 2002

IT **573703-27-2P 573703-31-8P 573703-34-1P**
573703-36-3P 573703-39-6P 573703-42-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tyrosine alkanediamide derivs. having μ-opioid binding affinity)

RN 573703-27-2 HCAPLUS
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

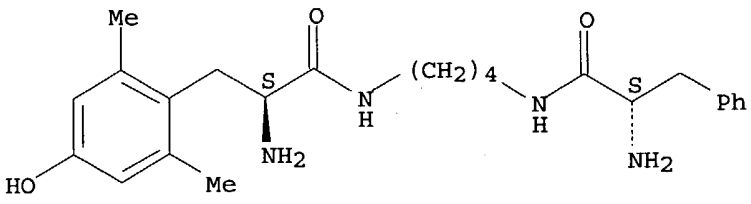
Absolute stereochemistry.



●2 HCl

RN 573703-31-8 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

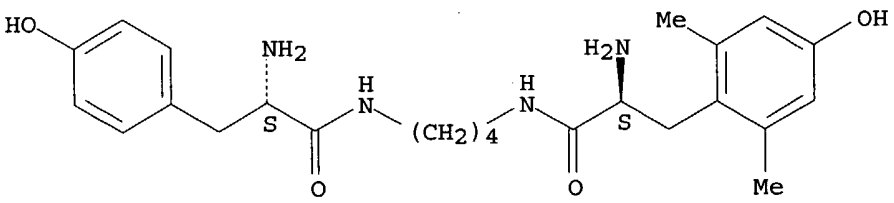
Absolute stereochemistry.



●2 HCl

RN 573703-34-1 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

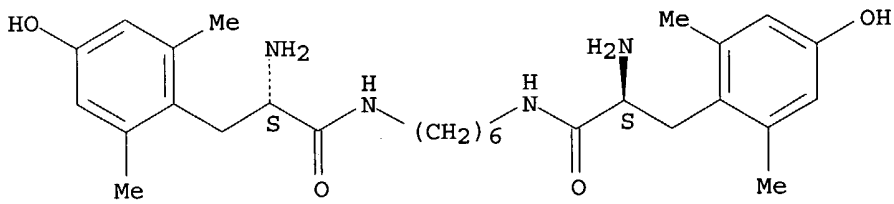
Absolute stereochemistry.



●2 HCl

RN 573703-36-3 HCAPLUS
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



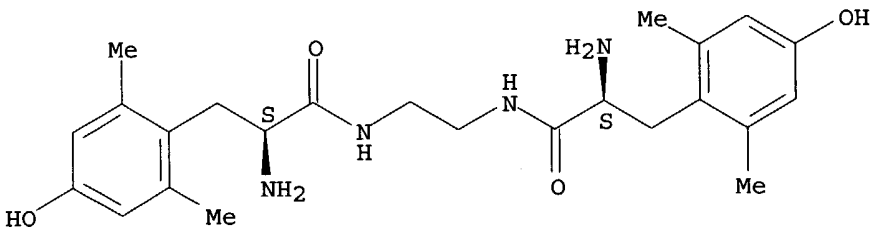
●2 HCl

RN 573703-39-6 HCAPLUS
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

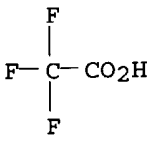
CRN 573703-38-5
CMF C24 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

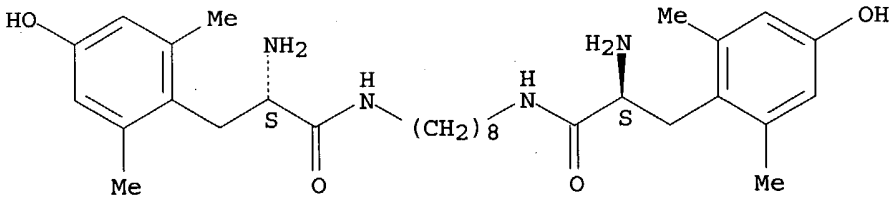


RN 573703-42-1 HCAPLUS
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

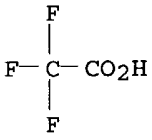
CRN 573703-41-0
CMF C30 H46 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



L34 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:459812 HCAPLUS
DN 139:173182
ED Entered STN: 17 Jun 2003
TI Unique High-Affinity Synthetic μ-Opioid Receptor Agonists with Central- and Systemic-Mediated Analgesia
AU **Okada, Yoshio**; **Tsuda, Yuko**; Fujita, Yoshio; **Yokoi, Toshio**; Sasaki, Yusuke; Ambo, Akihiro; Konishi, Ryoji; Nagata, Mitsuhiro; Salvadori, Severo; Jinsmaa, Yunden; **Bryant, Sharon D.**; **Lazarus, Lawrence H.**
CS Faculty of Pharmaceutical Sciences, Department of Medicinal Chemistry and High Technology Research Center, Kobe Gakuin University, Nishi, Kobe, 651-2180, Japan
SO Journal of Medicinal Chemistry (2003), 46(15), 3201-3209
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)

Section cross-reference(s): 34

AB Unique opioid mimetic substances containing identical N-terminal aromatic residues separated by an unbranched alkyl chain containing two to eight methylene groups were developed. Regardless of the length of interposing alkyl chain, the bis-Tyr and bis-Phe compds. were inactive; however, replacement by a single Dmt (2',6'-dimethyl-L-tyrosine) residue enhanced activity by orders of magnitude. Moreover, the bis-Dmt compds. were another 10-fold more potent with an optimum intra-aromatic ring distance of about four to six methylene units. 1,4-Bis(Dmt-NH)butane had high μ-opioid receptor affinity (Ki = 0.041 nM) and functional μ-opioid agonist bioactivity (IC50 = 5.3 nM) with in vivo central (intracerebroventricular) and systemic (s.c.) analgesia in mice (1.5- to 2.5-fold greater than and 10-12% relative to morphine, resp.); these activities were reversed by naloxone to the same degree. It appears that the bis-Dmt compds. indiscriminately act as both message and address domains.

ST mu opioid receptor agonist analgesic

IT Analgesics
Conformation
Molecular association
Molecular modeling
NMR (nuclear magnetic resonance)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Opioids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(μ-; preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Structure-activity relationship
(μ-opioid; preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(μ-opioid; preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT **577977-61-8 577977-65-2 577977-67-4**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT **573703-27-2P 573703-31-8P 573703-34-1P**
573703-36-3P 573703-42-1P 573703-44-3P 573703-46-5P
573703-52-3P 577977-87-8P 577977-88-9P 577977-89-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 76597-36-9 81638-49-5 **573703-38-5 573703-41-0**
573703-48-7 577977-56-1 **577977-70-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 107-15-3, 1,2-Diaminoethane, reactions 124-09-4, 1,6-Diaminohexane, reactions 373-44-4, 1,8-Diaminooctane 3978-80-1 35661-40-6
68076-36-8 99953-00-1 147688-40-2 573703-26-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists

with central- and systemic-mediated analgesia in relation to structure)

IT 110-60-1P, 1,4-Diaminobutane 81649-48-1P 573703-28-3P 573703-30-7P
573703-32-9P 573703-33-0P 573703-35-2P 573703-37-4P 573703-40-9P
573703-43-2P 573703-45-4P 573703-47-6P 573703-51-2P 577977-81-2P
577977-86-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

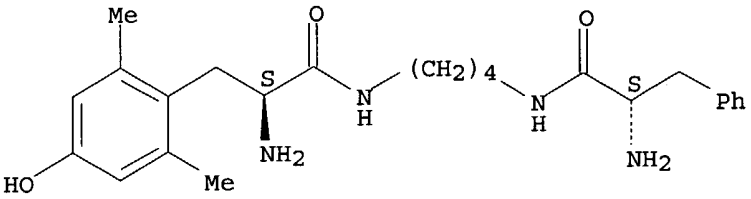
(1) Balboni, G; J Med Chem 2002, V45, P5556 HCAPLUS
(2) Balboni, G; J Med Chem 2002, V45, P713 HCAPLUS
(3) Bryant, S; Biol Chem 1997, V378, P107 HCAPLUS
(4) Bryant, S; J Am Chem Soc 1993, V115, P8503 HCAPLUS
(5) Bryant, S; J Med Chem 2002, V45, P5506 HCAPLUS
(6) Bryant, S; Peptides 2000 2001, P407 HCAPLUS
(7) Callahan, J; J Med Chem 1989, V32, P391 HCAPLUS
(8) Chandrakumar, N; J Med Chem 1992, V35, P223 HCAPLUS
(9) Cheng, Y; Biochem Pharmacol 1973, V22, P3099 HCAPLUS
(10) Dygos, J; Synthesis 1992, V8, P741
(11) Fujita, Y; Peptides:The Wave of the Future 2001, P616 HCAPLUS
(12) Goodman, M; NIDA Res Monogr 1993, V143, P195
(13) Guerrini, R; Eur J Pharmacol 1996, V302, P37 HCAPLUS
(14) Hansen, J; J Med Chem 1992, V35, P684
(15) Hughes, J; Nature 1975, V258, P577 HCAPLUS
(16) Iupac-Iub Commission On Biochemical Nomenclature; J Biol Chem 1985, V260, P14
(17) Lazarus, L; J Biol Chem 1989, V264, P354 HCAPLUS
(18) Lazarus, L; Prog Neurobiol 1993, V41, P473 HCAPLUS
(19) Lazarus, L; Prog Neurobiol 1999, V57, P377 HCAPLUS
(20) Melchiorri, P; Gen Pharmacol 1996, V27, P1099 HCAPLUS
(21) Meunier, J; Nature 1995, V377, P532 HCAPLUS
(22) Okada, Y; Chem Pharm Bull 1999, V47, P1193 HCAPLUS
(23) Okada, Y; Peptides:Frontiers of Peptide Science 1997, P660
(24) Okada, Y; Tetrahedron 1999, V55, P14391 HCAPLUS
(25) Portoghese, P; J Med Chem 1990, V33, P1714 HCAPLUS
(26) Portoghese, P; J Med Chem 1991, V34, P1715 HCAPLUS
(27) Portoghese, P; Trends Pharmacol Sci 1989, V10, P230 HCAPLUS
(28) Roques, B; Eur J Pharmacol 1979, V60, P109 HCAPLUS
(29) Salvadori, S; J Med Chem 1999, V42, P5010 HCAPLUS
(30) Salvadori, S; Mol Med 1995, V1, P678 HCAPLUS
(31) Sasaki, Y; Chem Pharm Bull 1999, V47, P1506 HCAPLUS
(32) Schiller, P; Biopolymers 1999, V51, P411 HCAPLUS
(33) Schiller, P; Eur J Med Chem 2000, V35, P895 HCAPLUS
(34) Schiller, P; J Med Chem 1999, V42, P3520 HCAPLUS
(35) Schiller, P; Proc Natl Acad Sci U S A 1992, V89, P11871 HCAPLUS
(36) Schwyzer, R; Ann N Y Acad Sci 1977, V297, P3 HCAPLUS
(37) Schwyzer, R; Biochemistry 1986, V25, P6335 HCAPLUS
(38) Shimohigashi, Y; Mol Pharmacol 1982, V21, P558 HCAPLUS
(39) Vaccarino, A; Peptides 2000, V21, P1975 HCAPLUS
(40) Zadina, J; Nature 1996, V386, P499
(41) Zadina, J; Neurosci Lett 1996, V215, P65 HCAPLUS

IT **577977-61-8 577977-65-2 577977-67-4**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

RN 577977-61-8 HCAPLUS

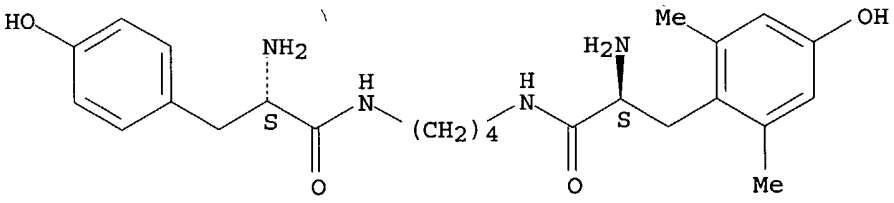
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



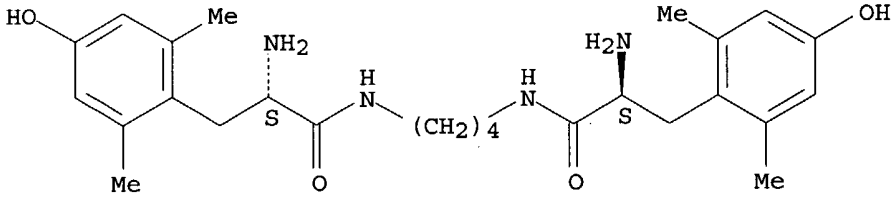
RN 577977-65-2 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



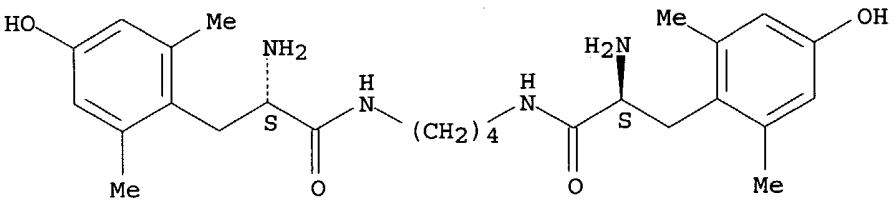
RN 577977-67-4 HCAPLUS
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **573703-27-2P 573703-31-8P 573703-34-1P**
573703-36-3P 573703-42-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)
RN 573703-27-2 HCAPLUS
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

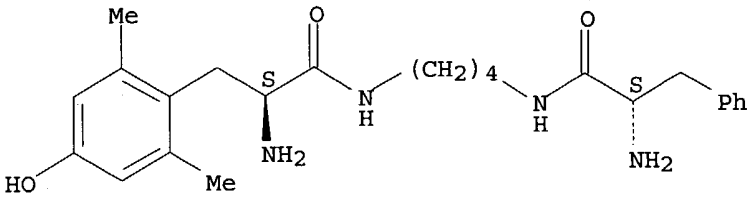
Absolute stereochemistry.



●2 HCl

RN 573703-31-8 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

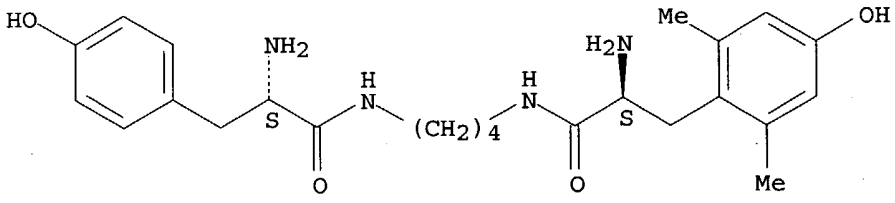
Absolute stereochemistry.



●2 HCl

RN 573703-34-1 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

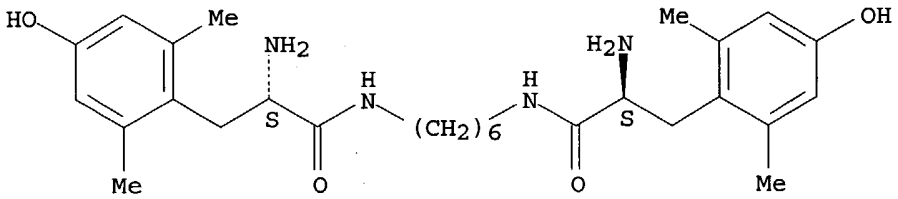
Absolute stereochemistry.



●2 HCl

RN 573703-36-3 HCAPLUS
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



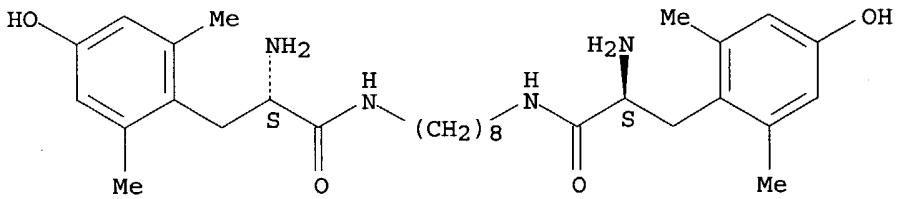
●2 HCl

RN 573703-42-1 HCAPLUS
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

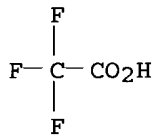
CRN 573703-41-0
CMF C30 H46 N4 O4

Absolute stereochemistry.



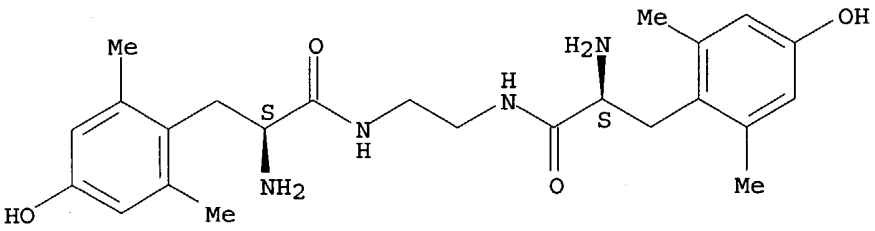
CM 2

CRN 76-05-1
CMF C2 H F3 O2



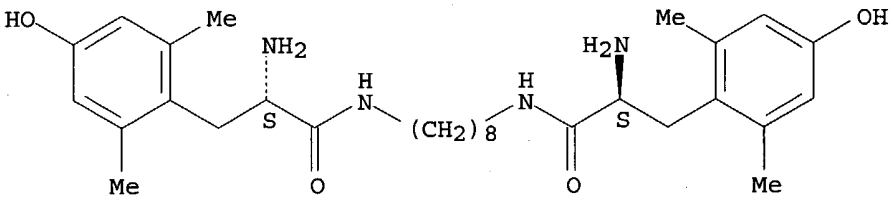
IT **573703-38-5 573703-41-0 577977-70-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)
RN 573703-38-5 HCAPLUS
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



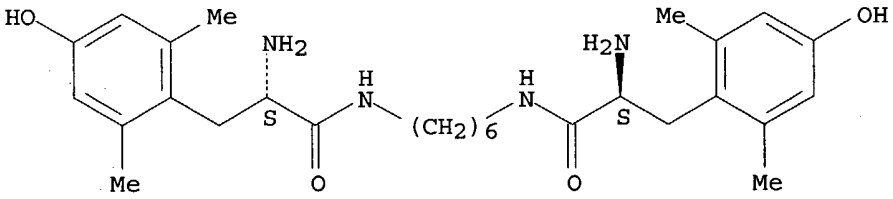
RN 573703-41-0 HCAPLUS
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 577977-70-9 HCAPLUS
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:449478 HCAPLUS
DN 140:128650
ED Entered STN: 12 Jun 2003
TI Design of opioid-mimetics: dimerization of 2', 6'-dimethyl-L-tyrosine
AU **Tsuda, Yuko**; Fujita, Yoshio; Miyazaki, Anna; Shiotani, Kimitaka; Fujisawa, Yutaka; **Yokoi, Toshio**; Li, Tingyou; Ambo, Akihiro; Sasaki, Yusuke; **Bryant, Sharon D.**; **Lazarus, Lawrence H.**; **Okada, Yoshio**
CS Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Nishi-ku, Kobe, 651-2180, Japan
SO Peptide Science (2003), Volume Date 2002, 39th, 105-108
CODEN: PSCIFQ; ISSN: 1344-7661
PB Japanese Peptide Society
DT Journal
LA English
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 2, 22
AB In order to obtain the potent and selective μ-agonists, dimerization of 2',6'-dimethyl-L-tyrosine (Dmt) was carried out. As a spacer, alkyldiamine and a pyrazinone ring (Pyr) platform extended with amino

groups were used. Opioid-mimetics Dmt-NH-(CH2)4-NH-Tyr and Dmt-NH-(Orn-Orn)-Pyr-NH-Dmt exhibited high μ-binding affinity, selectivity and fairly potent μ-agonism in vitro. Furthermore, Dmt-NH-(Orn-Orn)-Pyr-NH-Dmt had more potent antinociceptive activity than morphine after i.c.v. administration.

ST opioid mimetic pseudopeptide prepn antinociceptive conformation NMR simulation modeling; peptidomimetic opioid receptor binding structure activity analgesic; tyrosine dimethyl dimerization alkyldiamine pyrazinone tertiary structure CD

IT Structure-activity relationship
(analgesic; preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Conformation
(preparation and conformation by NMR and simulation and modeling of opioid-mimetics with antinociceptive activity)

IT Tertiary structure
(preparation and tertiary structure by simulation and modeling and CD of opioid-mimetics with antinociceptive activity)

IT Dimerization
(preparation of opioid-mimetics by dimerization of dimethylltyrosine using alkyldiamine or pyrazinone ring with amino groups as spacer)

IT Analgesics
Pain
(preparation of opioid-mimetics with antinociceptive activity by dimerization of dimethylltyrosine)

IT Peptidomimetics
(preparation of peptidomimetics, analgesic and opioid receptor-binding structure-activity relationship)

IT Simulation and Modeling, physicochemical
(preparation, conformation and tertiary structure by NMR, simulation and modeling, and CD of opioid-mimetics with antinociceptive activity)

IT Peptides, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pseudopeptides; preparation of pseudopeptides by dimerization of dimethylltyrosine using alkyldiamine or pyrazinone ring with amino groups as spacer)

IT Opioids
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(δ-; preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Structure-activity relationship
(δ-opioid receptor-binding; preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(δ-opioid; preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Opioids
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(μ-; preparation of opioid-mimetics by dimerization of dimethylltyrosine and their μ-opioid receptor-binding structure-activity relationship)

IT Structure-activity relationship
(μ-opioid receptor-binding; preparation of opioid-mimetics by

dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(μ-opioid; preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT 110449-60-0P 234450-16-9P 403476-93-7P 489473-59-8P 489473-60-1P
489473-61-2P 489473-62-3P 489473-63-4P 489473-64-5P
573703-31-8P 573703-34-1P 573703-36-3P
573703-44-3P 649757-27-7P **649757-28-8P** 649757-29-9P
649757-30-2P **649757-31-3P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT 234450-03-4 649757-32-4 649757-33-5 649757-34-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT **573703-27-2P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of opioid-mimetics by dimerization of dimethylltyrosine, their conformation, analgesic and opioid receptor-binding structure-activity relationship)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

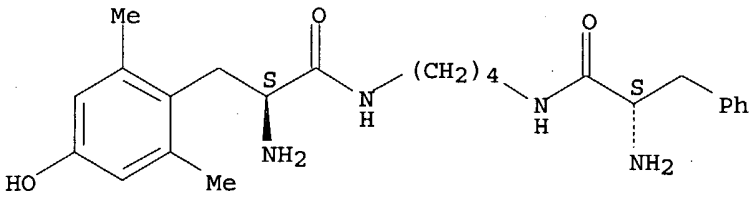
RE

(1) Costa, T; Life Sci 1982, V31, P1625 HCAPLUS
(2) Lazarus, L; J Biol Chem 1989, V264, P354 HCAPLUS
(3) Okada, Y; Biochem Biophys Res Commun 2000, V276, P7 HCAPLUS
(4) Okada, Y; Tetrahedron 1999, V55, P14391 HCAPLUS
(5) Zadina, J; Nature 1997, V386, P499 HCAPLUS

IT **573703-31-8P 573703-34-1P 573703-36-3P**
649757-28-8P 649757-31-3P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of opioid-mimetics by dimerization of dimethylltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

RN 573703-31-8 HCAPLUS
CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

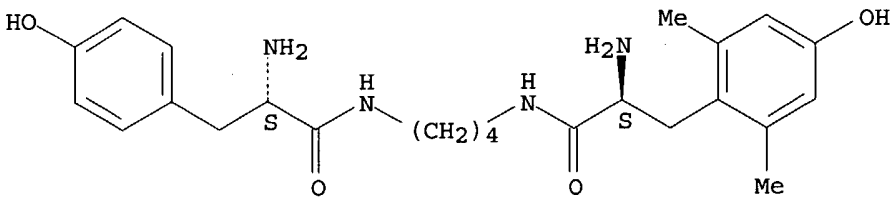


●2 HCl

RN 573703-34-1 HCAPLUS

CN Benzenepropanamide, α-amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

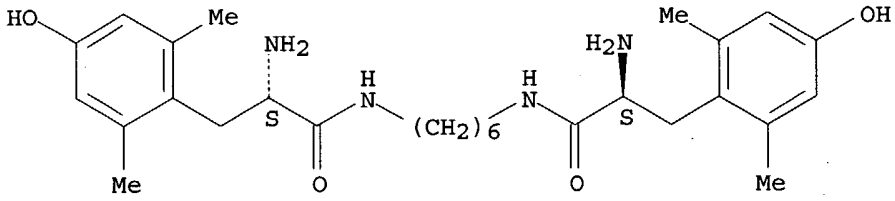
Absolute stereochemistry.



●2 HCl

RN 573703-36-3 HCAPLUS
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

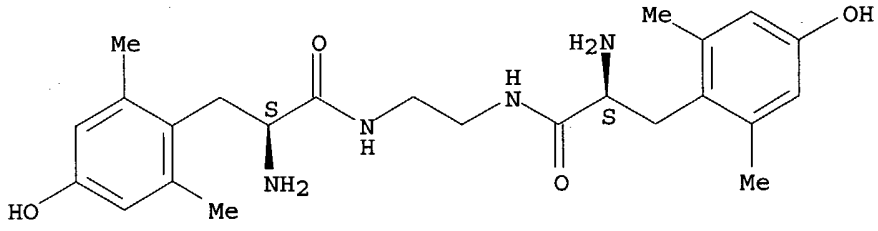
Absolute stereochemistry.



●2 HCl

RN 649757-28-8 HCAPLUS
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

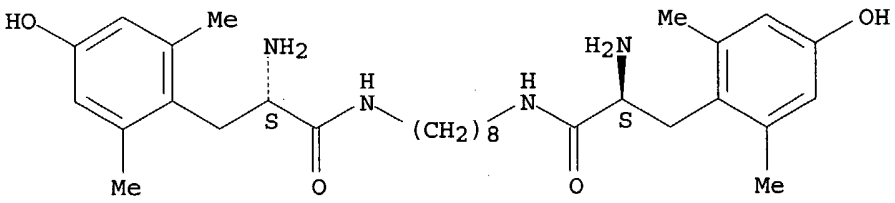
Absolute stereochemistry.



●2 HCl

RN 649757-31-3 HCAPLUS
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

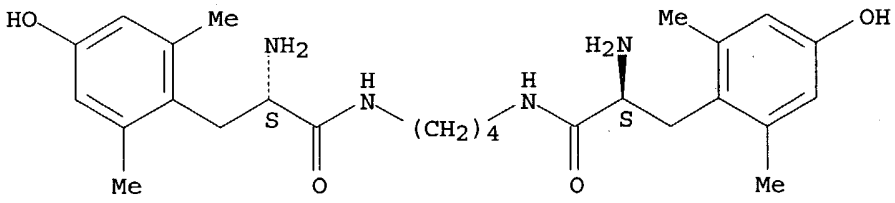
Absolute stereochemistry.



●2 HCl

IT **573703-27-2P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of opioid-mimetics by dimerization of dimethylltyrosine, their conformation, analgesic and opioid receptor-binding structure-activity relationship)
RN 573703-27-2 HCAPLUS
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

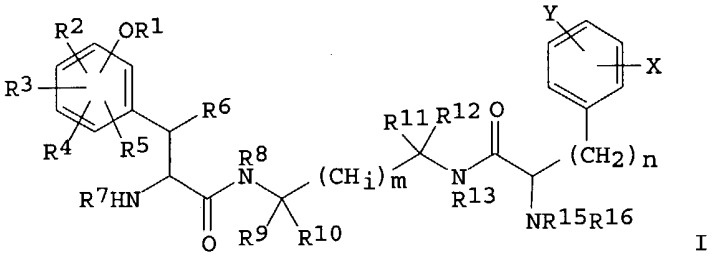


●2 HCl

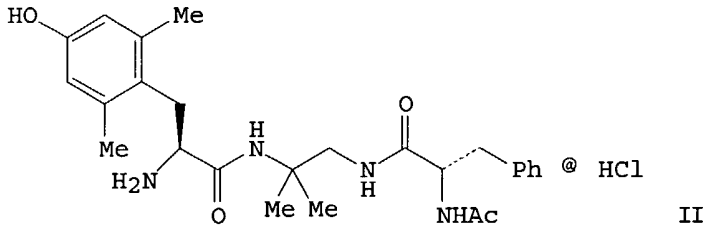
L34 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:534808 HCAPLUS
DN 121:134808
ED Entered STN: 17 Sep 1994
TI preparation of tyrosyl diamide derivatives as analgesics.
IN Hansen, Jr Donald W.; Chandrakumar, Nizal S.; Peterson, Karen B.; Tsymbalov, Sofya; Husa, Robert K.
PA G. D. Searle and Co., USA
SO U.S., 35 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-165
ICS A61K031-325; A61K031-17; C07C237-28
NCL 514487000
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5272175	A	19931221	US 1992-886276	19920520
	US 5364850	A	19941115	US 1993-125897	19930924

PRAI US 1992-886276 19920520
OS MARPAT 121:134808
GI



I



II

AB Title compds. [I; R1 = H, alkyl, Ac; R2-R6, R14, R15 = H, alkyl; R7 = H, Me3CO2C; R8-R13 = H, alkyl; R16 = H, Ac, COCF3, etc.; X = H, halo, alkyl; Y = H, alkyl; i = 0-2; m, n = 0-6; and cyclic forms thereof], were prepared Thus, tert-butoxycarbonyl-L-2,6-dimethyltyrosine and N-acetylphenylalanyl-NHCHCMe2NH2 were stirred with hydroxybenzotriazole and DCC in CH2Cl2 at 0°-room temperature overnight; the resulting coupling product was treated with 7 N HCl in dioxane to give title compound II. II was 7 times more active than the Jacobson compound in the mouse writhing assay, and showed μ and δ opiate receptor binding IC50 values of 0.4 and 0.3 nM, resp.

ST tyrosyl diamide prepn analgesic; peptide analog tyrosyl diamide analgesic

IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of tyrosyl diamide derivs. as analgesics)

IT Analgesics
(tyrosyl diamide derivs.)

IT 7764-95-6P, BOC-D-Ala-OH
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT 156892-50-1P 156892-51-2P 156892-52-3P 156892-53-4P 156892-54-5P
156892-55-6P 156892-56-7P 156892-57-8P **156892-58-9P**
156892-59-0P 156892-60-3P 156892-61-4P 156892-62-5P 156892-63-6P
156892-64-7P 156892-65-8P **156892-66-9P** 156892-67-0P
156892-68-1P 156892-69-2P 156892-70-5P 156892-71-6P 156892-72-7P
156892-73-8P 156892-74-9P 156892-75-0P 156892-76-1P 156892-77-2P
156892-78-3P 156892-79-4P 156892-80-7P 156892-81-8P 156892-92-1P
156892-93-2P 156892-94-3P 156892-95-4P 156892-96-5P 156892-97-6P
156892-98-7P 156892-99-8P 156893-00-4P 156893-01-5P 156893-02-6P
156893-03-7P 156893-04-8P 156893-06-0P 156893-07-1P 156893-09-3P
156893-10-6P 156893-13-9P 156893-14-0P 156893-15-1P 156893-16-2P
156893-17-3P 156893-18-4P 156893-19-5P 156893-20-8P 156893-21-9P
156893-22-0P **156893-23-1P** 156893-24-2P **156893-25-3P**
156893-26-4P 156893-27-5P 156893-28-6P 156893-29-7P 156893-30-0P
156893-31-1P 156893-32-2P 156893-33-3P 156893-34-4P 156893-35-5P

156893-36-6P 156893-37-7P 156893-38-8P 156893-39-9P 156893-42-4P
156893-43-5P 157006-64-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as analgesic)

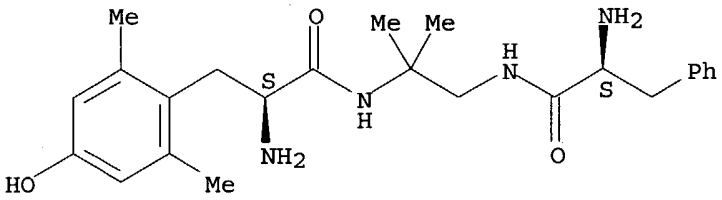
IT 92502-12-0P 99953-00-1P 100927-10-4P 126312-80-9P 140866-04-2P
145235-85-4P 156892-82-9P 156892-83-0P 156892-84-1P 156892-85-2P
156892-86-3P 156892-87-4P 156892-88-5P 156892-89-6P 156892-90-9P
156892-91-0P 156893-05-9P 156893-08-2P 156893-11-7P 156893-12-8P
156893-40-2P 156893-41-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for analgesic)

IT 99-09-2, m-Nitroaniline 107-15-3, 1,2-Ethanediamine, reactions
330-81-4 407-25-0, Trifluoroacetic anhydride 624-83-9, Methyl isocyanate 811-93-8, 1,2-Diamino-2-methylpropane 1161-13-3, Z-Phe-OH
1476-23-9, Allyl isocyanate 2018-61-3 2759-28-6 2949-22-6, Ethyl isocyanatoacetate 3173-56-6, Benzyl isocyanate 3978-80-1, BOC-Tyr-OH
17543-58-7 18471-40-4, 1-Benzyl-3-aminopyrrolidine 35356-70-8, Methyl 2-acetamidoacrylate 42429-20-9 96613-91-1 97268-59-2 99953-00-1
120687-57-2 145235-84-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of tyrosyl diamide analgesic)

IT **156892-58-9P 156892-66-9P 156893-23-1P**
156893-25-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as analgesic)

RN 156892-58-9 HCAPLUS
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

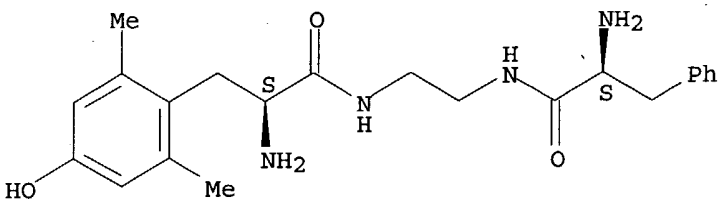
Absolute stereochemistry.



●2 HCl

RN 156892-66-9 HCAPLUS
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

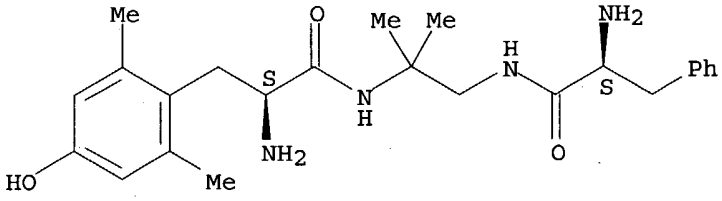
Absolute stereochemistry.



●2 HCl

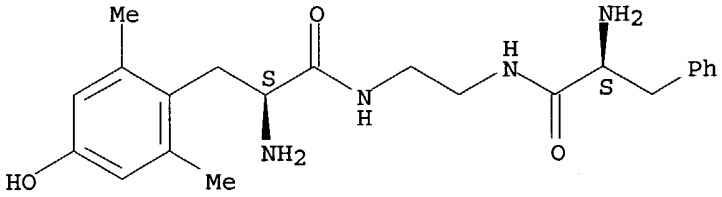
RN 156893-23-1 HCAPLUS
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156893-25-3 HCAPLUS
CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=>